

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Application of: Gregory T. Bleck, et al.	Conf. No. 9065
Serial No.: 10/759,315	Group No.: 1633
Filed: January 16, 2004	Examiner: Popa
Entitled: <b>PRODUCTION OF HOST CELLS CONTAINING MULTIPLE INTEGRATING VECTORS BY SERIAL TRANSDUCTION</b>	

**PRE-APPEAL BRIEF REQUEST FOR REVIEW**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Dear Examiner Popa:

Applicants request a Pre-Appeal Brief Conference for the above-identified application. This paper is submitted along with a Notice of Appeal in compliance with 37 CFR 41.31 and the Pre-Appeal Brief Conference form PTO/SB/33. The Commissioner is hereby authorized to charge any fees during the entire pendency of this application, including fees due under 37 C.F.R. §§ 1.16 and 1.17 that may be required, including any required extension of time fees, or credit any overpayment to **Deposit Account 50-4302**, referencing **Attorney Docket No. GALA-08484**. The argument in support of this request follows.

**BASIS FOR REVIEW**

Claims 1-10, 12, 14-18, 20-26, 28 and 30-41 are pending in the present application and rejected as allegedly being obvious. In the Final Office Action dated Dec. 21, 2010, Claims 1-10, 12, 14, 18, 20, 21, 28, 30-34, and 41 are rejected under 35 U.S.C. § 103, as allegedly being obvious over Mathor et al. in view of each of Burns et al., Felts et al.; Schott et al.; and Persons et al. (Rejection 1); Claims 1-10, 12, 14, 18, 20, 21, 28, 30-34, and 41 are rejected under 35 U.S.C. § 103, as allegedly being obvious over Mathor et al. in view of each of Burns et al., Felts et al.; Schott et al.; and Persons et al., in view of Schroder et al. (Rejection 2); Claims 1-10, 12, 14, 18, 20, 21, 28, 30-34, and 41 are rejected under 35 U.S.C. § 103, as allegedly being obvious over Mathor et al. in view of each of Burns et al., Felts et al.; Schott et al.; and Persons et al. in further view of Primus et al. and Kolb et al. (Rejection 3); Claims 1-10, 12, 14, 18, 20, 21, 28, 30-34, and 41 are rejected under 35 U.S.C. § 103, as allegedly being obvious over Mathor et al. in view of each of Burns et al., Felts et al.; Schott et al.; and Persons et al. in further view of

Naldini et al. (Rejection 4). This request focuses on Rejection 1 as the arguments being presented for Rejection 1 also apply to Rejections 2, 3 and 4 as those rejections incorporate Rejection 1.

**1. The Examiner has committed error by not considering factual evidence presented by Applicants**

As held in *In re Sullivan*, 498 F. 3d 1345, 1351, 81 USPQ2d 1034 (Fed. Cir. 2007):

Rebuttal evidence is “merely a showing of facts supporting the opposite conclusion.” *In re Piasecki*, 745 F.2d 1468, 1472 (Fed.Cir.1984). Evidence rebutting a *prima facie* case of obviousness can include: “evidence of unexpected results,” *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1369 (Fed.Cir.2007), evidence “that the prior art teaches away from the claimed invention in any material respect,” *In re Peterson*, 315 F.3d 1325, 1331 (Fed.Cir.2003), and evidence of secondary considerations, such as commercial success and long-felt but unresolved needs, *WMS Gaming, Inc. v. Int'l Game Tech.*, 184 F.3d 1339, 1359 (Fed.Cir.1999).

*Id.* Importantly, when a patent applicant puts forth rebuttal evidence, the Office must consider that evidence. *Id.*, see also *In re Soni*, 54 F.3d 746, 750 (Fed.Cir.1995) (stating that “all evidence of nonobviousness must be considered when assessing patentability”); *In re Sernaker*, 702 F.2d 989, 996 (Fed.Cir.1983). Furthermore, a primary step in the obviousness analysis is to “determine whether there was an apparent reason to combine the known elements in the fashion claimed.” *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). A rejection for obviousness must include “articulated reasoning **with some rational underpinning** to support the legal conclusion.” *Id.*, quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)(Emphasis added). The proper question to ask is whether a person of ordinary skill in the art would have seen a benefit to combining the prior art teachings. *KSR*, 550 U.S. at 424.

In the response dated Oct. 7, 2010 and in the Fourth and Fifth Declarations of Dr. Gregory Bleck (submitted Dec. 17, 2009 and Oct. 7, 2010, respectively), Applicant’s submitted extensive evidence as to why the Examiner’s conclusions regarding both the primary prior art reference (Mathor et al.) and the secondary references were not scientifically supportable and based on a rational underpinning. The Examiner has failed to consider this evidence.

At page 7 of the current Office Action, the Examiner states that Mathor et al. teach that protein expression is directly proportional to integration events (i.e., copy number)(p. 10376, column 1). The Examiner goes on to state that:

“It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Mathor et al. and Burns et al. by serially transducing their cells with high MOIs (such as MOIs of 1,000) to achieve the claimed ranges of integration events, with a reasonable expectation of success. The motivation to do so is provided by Mathor et al., who teach the possibility of specifying the level of transgene expression by controlling the integration events (Abstract, p. 10376, column 1).

Office Action, p. 8. The Examiner cites the abstract and p. 10376 of Mathor. Mathor et al. state in this section that “The rate of secretion of the exogenous protein by cultures generated by single clones was proportional to the number of integrations per progenitor cell.” In sum, the Examiner is arguing that based on the results of Mathor et al., one of skill in the art would be motivated to make cells with greater than 20 integrated retroviral vectors because the rate of protein production is proportional to the number of integrations. **This is the same rejection the Examiner has relied upon in multiple office actions even though Applicants have submitted rebuttal evidence as to why the Examiner’s conclusions regarding the primary and secondary references are not scientifically supportable.**

Here is a short summary of that evidence (see Applicants response dated Oct. 7, 2010, pages 8-12 for a complete discussion of the evidence as supported by the Fifth Bleck Decl.):

- Mathor et al. presents the data on proviral integration and transgene expression on p. 10373 and in Table 1. Fifth Bleck Decl. ¶5.
- This data shows increasing transgene expression as the proviral integrations increase from 1 to 8. When the number of proviral integrations increases to 15, the transgene expression actually decreases to a level lower than was observed with 8 integrations. Id.
- Mathor’s statement that: “The rate of secretion of the exogenous protein by cultures generated by single clones was proportional to the number of integrations per progenitor cell” is valid with respect to the range of 1 to 8 integrations and does not apply outside of that range. Id.
- The Examiner’s attempt to apply the statement outside of the range is not factually supported, i.e., supported by the data. Fifth Bleck Decl. ¶5.
- The experiments in Mathor et al. were not conducted in a manner so that a statistical analysis could be conducted. See Mathor et al., particularly p. 10373, Fifth Bleck Decl. ¶7. The groups were not replicated and there is no way to determine experimental error. Id. Thus, it is not possible to construct a curve or equation from the data so that a

correlation of transgene expression to a number of integrations outside of the data range (i.e., to 20 to 100 integrations as claimed) can be made. Id.

The Examiner argues that one of skill in the art would know that individual clones could have higher expression than was observed for the 15 integrant clone in Mathor et al. As argued by the Examiner: "One of skill in the art would have known that it is statistically probable to obtain clones which, albeit having the same number of retroviral copies inserted into their chromosomes, express different amounts of retroviral-encoded proteins." Applicants agree that clones having the same number of integrations can express different levels of a protein. However, to use that as a basis for arguing that Mathor et al. would lead a person of skill in the art to produce clones with more than 20 integrations is simply not scientifically supported by Mathor et al. **The data in Mathor et al. clearly shows that expression decreased after 8 integrations.** In particular, the expression for a clone with 15 integrations was lower than expression from clones with 8 integrations. Applicants fail to understand how this can be seen as support for increasing the number of integrations to greater than 20.

Thus, Applicants respectfully submit that the Examiner has committed clear error because the Examiner has failed to consider evidence that the references do not provide a rational underpinning for the rejection. **There is no basis in the cited references for predicting whether expression by a single clone other than those described in the references would be substantially higher or lower on average.** The data in the papers cited by the Examiner is simply not amenable to that type of prediction based on scientifically acceptable statistical methods. What if the clones measured in the cited references were outliers and exhibited the highest possible level of protein expression? Without more data, this conclusion is just as hard to support as the Examiner's conclusion that some clones would have higher protein expression.

**2. The Examiner has committed error by not considering evidence that the prior art as a whole teaches away from the claimed invention**

The Examiner has also failed to consider Applicants evidence concerning references in the prior art that teach away from the invention as claimed. Applicants have cited multiple references that establish that at the time of the claimed invention the state of the art was that: 1) cells have a host defense mechanism that inactivates newly introduced, invading sequences such

as retroviral vectors; 2) the host defense mechanism operates by methylation of the invading sequences, which causes transcriptional inactivation of the sequences; 3) transcriptional inactivation by methylation leads to reduced expression from retroviral vectors; 4) the inactivation may be triggered by structures formed during integration of the retroviral vectors; and 5) the presence of multiple repeats of an invading sequence such as a retroviral vector triggers methylation and inactivation. Fifth Black Decl., ¶ 8-9; See Response dated October 7, 2010 p. 12-18 for a complete discussion.<sup>1</sup>

These facts establish the state of the art. The Examiner has failed to consider or give proper weight to this evidence. Applicants respectfully submit the totality of the prior art must be considered, and that proceeding contrary to the accepted wisdom in the art is evidence of non-obviousness. MPEP §2145. Applicants further submit that predictability as discussed in KSR encompasses the expectation that prior art elements are capable of being combined, as well as the expectation that the combination would have worked for its intended purpose. An inference that a claimed combination would not have been obvious is especially strong where the prior art's teachings undermine the very reason being proffered as to why a person of ordinary skill would have combined the known elements. *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314 (Fed. Cir. 2009). This is especially applicable to the case at hand, where the prior art teaches that increasing retroviral integrations can cause inactivation of the retroviral transgene and thus decreased expression of the protein of interest.

Applicants respectfully request that the rejection of the Claims under 35 U.S.C. § 103(a) be withdrawn and that the claims be passed to allowance without further delay.

Dated: June 16, 2011

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<sup>1</sup> See also Bestor and Tycko 1996 (Tab 1 to the Fifth Black Decl.), Garrick et al. 1998 (Tab 2 to the Fifth Black Decl.); Cherry et al. 2000 (Tab 3 to the Fifth Black Decl.); Mehtali et al. 1990 (Tab 4 to the Fifth Black Decl.); Niwa et al. 1983 (Tab 5 to the Fifth Black Decl.); Svoboda et al. 2000 (Tab 6 to the Fifth Black Decl.); Ellis and Pannell 2001 (Tab 7 to the Fifth Black Decl.); Challita and Kohn 1994 (attached at Tab 8 to the Fifth Black Decl.)